C5	0.1570 (8)	0.698 (4)	0.475 (1)	0.048 (7)
C6	0.1198 (9)	0.851 (4)	0.464 (1)	0.050 (7)
C7	0.1346 (10)	1.003 (4)	0.526 (1)	0.055 (8)
C8	0.1814 (8)	0.988 (4)	0.598 (1)	0.058 (8)
C9	0.3216 (9)	0.322 (5)	0.665 (2)	0.073 (9)
C11	0.3956 (9)	0.160 (5)	0.771 (1)	0.087 (10)
C12	0.432 (1)	0.198 (4)	0.854 (2)	0.17 (1)
C13	0.070 (1)	0.835 (7)	0.381 (2)	0.09 (1)
C14	0.093 (2)	1.163 (7)	0.520 (2)	0.10 (1)
F13A	0.0688 (7)	0.706 (3)	0.334 (1)	0.19 (1)
F13B	0.0299 (6)	0.825 (4)	0.3952 (9)	0.17 (1)
F13C	0.0605 (8)	0.994 (3)	0.334 (1)	0.18 (1)
F14A	0.0503 (6)	1.126 (2)	0.513 (1)	0.14 (1)
F14B	0.1160 (7)	1.293 (3)	0.579 (1)	0.22 (1)
F14C	0.0860 (7)	1.276 (3)	0.451 (1)	0.14 (1)

Table 2. *Selected geometric parameters* (Å, °)

O2—C1	1.40 (2)	C4—C4a	1.42 (2)
O2—C3	1.36 (2)	C4a—C5	1.39 (2)
C1a—C8	1.38 (2)	C5—C6	1.40 (2)
C3—C4	1.34 (2)	C6—C7	1.41 (2)
C3—C9	1.55 (3)	C7—C8	1.36 (2)
C1—O2—C3	122 (2)	C1a—C4a—C4	116 (2)
O1—C1—O2	114 (2)	C1a—C4a—C5	118 (2)
O2—C1—C1a	115 (3)	C4—C4a—C5	126 (3)
C1—C1a—C4a	123 (3)	C4a—C5—C6	121 (2)
C1—C1a—C8	117 (3)	C5—C6—C7	118 (2)
C4a—C1a—C8	120 (2)	C6—C7—C8	120 (3)
O2—C3—C4	121 (2)	C1a—C8—C7	122 (3)
C3—C4—C4a	123 (2)		

The low number of significant reflections meant that only the peripheral atoms could be refined anisotropically. The high vibrational amplitudes displayed by the terminal groups, possibly an indication of disorder, explained the low number of observed reflections and the relatively high R factor of 0.096 obtained when all 2002 independent reflections were used.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *TEXSAN LS*. Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *TEXSAN FINISH*. Literature survey: *CSSR* (1984).

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: LI1134). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Structural Studies of Intermediates in the Synthesis of Mifepristone (RU 486). IV. An α-Epoxy Steroid

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Abstract

Crystallographic characterization of the title compound, $5\alpha,10\alpha$-epoxy-3,3-ethylenedioxy-17β-hydroxy-17α-(1-propynyl)-9(11)-estrene, $C_{23}H_{30}O_4$, establishes the configuration of the epoxy O atom as $5\alpha,10\alpha$ and locates the double bond between C9 and C11. The asymmetric unit contains two crystallographically independent molecules which are related by a pseudo twofold screw axis. The presence of an epoxy O atom between C5 and C10 causes strain in the molecules, and this is reflected in the distortion of bond angles around several tetrahedral C atoms. The propynyl group is oriented perpendicular to the steroid skeleton. The molecular structure is stabilized by a network of O—H···O hydrogen bonds.

Comment

The title $5\alpha,10\alpha$-epoxy steroid, (III), is a key intermediate in the synthesis of mifepristone (RU 486), (I), the first steroidal antiprogesterone drug for non-surgical abortion in clinical use (Ulmann & Dubois, 1989; Heikinheimo, Ylikorkala & Lahteenmaki, 1990). The antagonistic activity of RU 486 is due to the 11β-dimethylaminophenyl substitution (Benhamou *et al.*, 1992). Crystallographic characterization has established the configuration of the epoxy O atom as $5\alpha,10\alpha$ and has located the double bond between C9 and C11. Fig. 1 depicts the conformation of the two crystallographically independent molecules, 1 and 2, present in the asymmetric unit, which are related by a pseudo twofold screw axis. The bond distances, angles and relevant torsion angles are in satisfactory agreement with accepted values (Duax, Griffin, Strong & Wood, 1989). The high e.s.d.'s of the bond lengths may be due to the poor ratio of the number of observations to parameters, a consequence of having two molecules in the asymmetric unit and the relatively weak diffracting properties of the crystal. That

the presence of an epoxy O atom between C5 and C10 causes strain in the molecule is quite apparent from the distortion of bond angles around several tetrahedral C atoms (in rings A and B).

RU 486 (I)

(II)

(III)   (IV)   (V)   (VI)
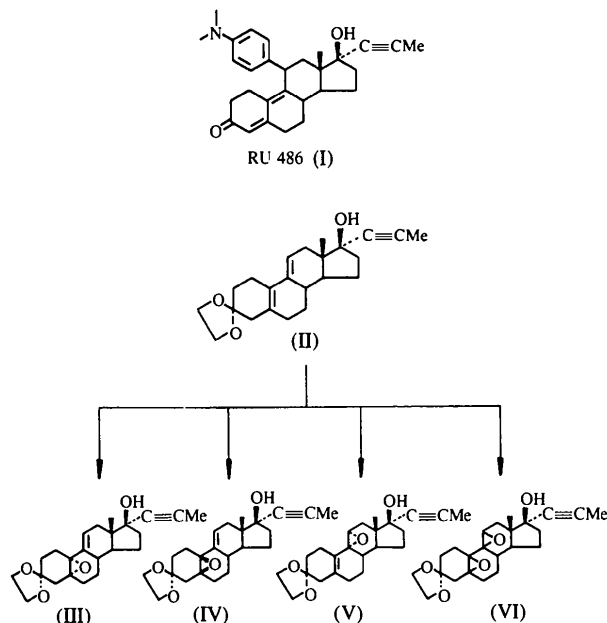
The two independent molecules are conformationally similar except for the B rings; the difference is reflected in the significant difference in the endocyclic torsion angles. In molecule 1, ring B assumes a distorted 7α,8β-half-chair conformation [asymmetry parameter $\Delta C_2(C7,C8)$ = 9.80°; Duax & Norton, 1975], whereas it adopts a 7β-sofa conformation [$\Delta C_s(C7)$ = 6.57°] in molecule 2. Each A ring has an approximate sofa conformation [$\Delta C_s(C2)$ = 7.88 and 7.71°]. The C rings have half-chair conformations [$\Delta C_2(C13,C14)$ = 2.30 and 3.61°] and each five-membered D ring adopts the commonly found 13-envelope conformation [$\Delta C_s(C13)$ = 1.11 and 4.03°]. The dihedral angles between the least-squares planes of rings A and D (23.2 and 17.1°) indicate a slight folding of the molecules, which may be attributed to the steric interactions. The non-bonded distances between O2 and O4, generally believed to be important in drug–receptor interactions, are 10.97 and 11.09 Å for molecules 1 and 2, respectively, of the title compound, 10.96 in RU486 (van Geerestein, Kanters, van der Sluis & Kroon, 1986), 10.82 in ORG 761, an analogue of RU 486 (van Geerestein, Kanters & Kroon, 1987), 10.27 in an 11β-substituted derivative of RU 486 (Bidyasagar, Ravikumar, Rama Rao, Reddy & Singh, 1994) and 11.02 Å in a β-epoxy steroid (Bidyasagar, Ravikumar, Rama Rao, Reddy & Singh, 1995). The perpendicular orientation of the propynyl group is defined by the torsion angle C15—C16—C17—C19, which is −91.6 (7) in molecule 1 and −93.0 (6)° in molecule 2; these angles are similar to those found in
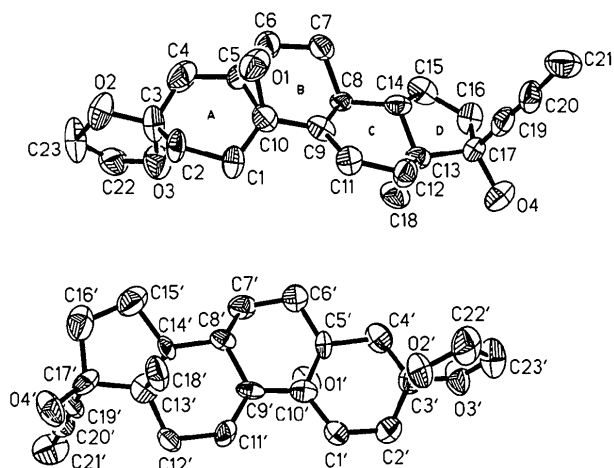

Fig. 1. Perspective view of the two independent molecules of 3,3-ethylenedioxy-17β-hydroxy-17α-(1-propynyl)-5α,10α-epoxy-9(11)-estrene in the asymmetric unit, with the atom-numbering scheme. Displacement ellipsoids are plotted at the 50% probability level. The H atoms have been omitted for clarity.

RU 486 [−93.8 (4)°], ORG 761 [−103.3 (5)°], the 11β-substituted steroid [96.7 (6)°] and the β-epoxy steroid [94.6 (5)°].

The crystal packing is shown in Fig. 2. The two crystallographically independent molecules are related by a pseudo twofold screw axis running parallel to the *a* axis, positioned at approximately (0, 1/2, 1/4) or (0, 1/2, 3/4). There is no hydrogen bonding linking the two independent molecules. However, both molecules are involved in an O—H···O hydrogen-bonding network involving the hydroxy group and the screw-related [−*x* + 1, *y* − 1/2, −*z* for molecule 1, −*x* + 2, *y* + 1/2, −*z* + 1 for molecule 2] epoxy O atom [O···O 2.880 (6), 2.813 (9) Å; H(O)···O 2.032 (6), 1.972 (9) Å and O—H(O)···O 174.4 (7), 169.7 (7)°].
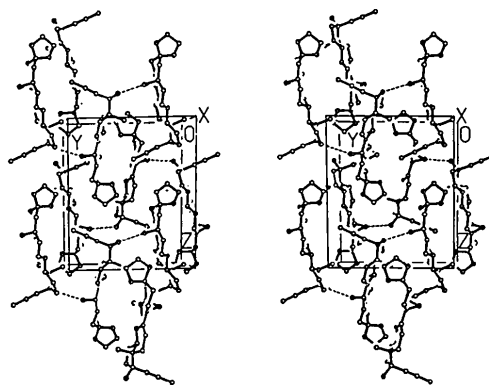

Fig. 2. Stereoscopic illustration of the molecular packing in the unit cell viewed down the *a* axis.

Experimental

The most convenient method for introducing 11β-(dimethyl-amino)phenyl substitution at the 11β position of a 19-norsteroid is the epoxidation of 5(10),9(11)-estradienes, (II), which yields mainly the desired 5α,10α-epoxide, (III), along with smaller amounts of 5β,10β, (IV), 9α,11α, (V), and diepoxide, (VI), isomers (see scheme above). The title compound, (III), was prepared by the method in the literature (Gasc & Nedelec, 1971) and recrystallization from ethyl acetate afforded pale yellow platelets (with great difficulty).

Crystal data

$C_{23}H_{30}O_4$	Mo $K\alpha$ radiation
$M_r = 370.5$	$\lambda = 0.71073$ Å
Monoclinic	Cell parameters from 25
$P2_1$	reflections
$a = 11.203$ (2) Å	$\theta = 6\text{--}15°$
$b = 12.368$ (2) Å	$\mu = 0.076$ mm^{-1}
$c = 14.849$ (3) Å	$T = 293$ K
$\beta = 99.8$ (2)°	Platelet
$V = 2027.2$ (6) Å^3	$0.15 \times 0.13 \times 0.12$ mm
$Z = 4$	Pale yellow
$D_x = 1.214$ Mg m^{-3}	

Data collection

Siemens $R3m/V$ diffractometer	$R_{int} = 0.025$
	$\theta_{max} = 22.5°$
$\omega/2\theta$ scans	$h = 0 \rightarrow 12$
Absorption correction:	$k = 0 \rightarrow 13$
none	$l = -16 \rightarrow 16$
2983 measured reflections	2 standard reflections
2811 independent reflections	monitored every 98
1442 observed reflections	reflections
$[I > 3\sigma(I)]$	intensity decay: $<1\%$

Refinement

Refinement on F	$(\Delta/\sigma)_{max} = 0.005$
$R = 0.050$	$\Delta\rho_{max} = 0.152$ e Å^{-3}
$wR = 0.053$	$\Delta\rho_{min} = -0.158$ e Å^{-3}
$S = 0.992$	Extinction correction: none
1442 reflections	Atomic scattering factors
487 parameters	from $SHELXTL\text{-}Plus$
$w = 1/[\sigma^2(F) + 0.0038F^2]$	(Sheldrick, 1990)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O1	0.4330 (5)	0.8658	0.2353 (4)	0.066 (3)
O2	0.4569 (5)	0.7645 (5)	0.5114 (4)	0.061 (5)
O3	0.5062 (5)	0.6217 (5)	0.4293 (3)	0.071 (4)
O4	0.6360 (5)	0.5821 (4)	-0.1764 (3)	0.068 (3)
C1	0.6116 (6)	0.7562 (6)	0.3058 (5)	0.048 (4)
C2	0.5828 (6)	0.7920 (6)	0.3976 (5)	0.051 (4)
C3	0.4775 (6)	0.7337 (6)	0.4235 (5)	0.058 (2)
C4	0.3627 (6)	0.7510 (6)	0.3547 (4)	0.069 (6)
C5	0.3808 (6)	0.7609 (6)	0.2561 (5)	0.052 (5)
C6	0.2691 (5)	0.7281 (6)	0.1842 (5)	0.058 (5)
C7	0.2926 (5)	0.7388 (6)	0.0888 (5)	0.050 (4)
C8	0.4093 (6)	0.6838 (6)	0.0738 (5)	0.041 (4)
C9	0.5188 (6)	0.7348 (6)	0.1335 (5)	0.040 (4)
C10	0.5046 (6)	0.7659 (6)	0.2312 (5)	0.051 (5)
C11	0.6230 (6)	0.7527 (6)	0.1053 (6)	0.047 (4)
C12	0.6484 (6)	0.7257 (6)	0.0111 (5)	0.050 (4)
C13	0.5557 (6)	0.6468 (6)	-0.0383 (5)	0.042 (4)
C14	0.4287 (6)	0.6833 (5)	-0.0267 (5)	0.046 (4)
C15	0.3410 (6)	0.6159 (6)	-0.0969 (5)	0.055 (4)
C16	0.4113 (6)	0.5888 (6)	-0.1734 (5)	0.055 (5)
C17	0.5380 (6)	0.6402 (6)	-0.1459 (5)	0.051 (4)
C18	0.5824 (6)	0.5305 (6)	0.0014 (5)	0.065 (5)
C19	0.5423 (5)	0.7522 (6)	-0.1836 (5)	0.051 (5)
C20	0.5415 (6)	0.8379 (6)	-0.2210 (5)	0.052 (5)
C21	0.5400 (7)	0.9447 (6)	-0.2614 (5)	0.071 (5)
C22	0.4719 (6)	0.5848 (7)	0.5078 (5)	0.085 (5)
C23	0.4702 (7)	0.6770 (7)	0.5667 (5)	0.060 (5)
O1'	0.9474 (5)	0.2823 (5)	0.2596 (4)	0.056 (3)
O2'	1.0439 (5)	0.5157 (5)	0.0798 (4)	0.062 (3)
O3'	1.0024 (5)	0.3651 (5)	-0.0105 (3)	0.068 (4)
O4'	1.0951 (5)	0.5591 (5)	0.7276 (4)	0.067 (3)
C1'	1.1321 (6)	0.3872 (6)	0.2414 (5)	0.052 (5)
C2'	1.1173 (6)	0.3480 (6)	0.1407 (5)	0.059 (5)
C3'	1.0147 (6)	0.4030 (6)	0.0812 (5)	0.053 (5)
C4'	0.8931 (6)	0.3885 (6)	0.1149 (5)	0.060 (5)
C5'	0.8991 (5)	0.3826 (6)	0.2197 (5)	0.039 (4)
C6'	0.7853 (5)	0.4164 (6)	0.2522 (5)	0.052 (4)
C7'	0.7939 (6)	0.4036 (6)	0.3541 (4)	0.056 (5)
C8'	0.9070 (5)	0.4614 (6)	0.4065 (5)	0.037 (4)
C9'	1.0217 (6)	0.4185 (6)	0.3775 (5)	0.037 (4)
C10'	1.0170 (6)	0.3824 (6)	0.2794 (5)	0.043 (3)
C11'	1.1220 (6)	0.4075 (6)	0.4397 (5)	0.044 (4)
C12'	1.1390 (6)	0.4345 (6)	0.5408 (5)	0.047 (4)
C13'	1.0354 (6)	0.5030 (6)	0.5630 (4)	0.046 (4)
C14'	0.9148 (6)	0.4573 (6)	0.5098 (5)	0.039 (4)
C15'	0.8176 (6)	0.5172 (6)	0.5530 (5)	0.070 (5)
C16'	0.8788 (6)	0.5397 (6)	0.6511 (4)	0.067 (5)
C17'	1.0092 (6)	0.4998 (6)	0.6630 (5)	0.045 (5)
C18'	1.0549 (6)	0.6189 (6)	0.5359 (4)	0.058 (5)
C19'	1.0171 (5)	0.3865 (6)	0.6985 (4)	0.046 (5)
C20'	1.0281 (6)	0.2972 (6)	0.7295 (5)	0.047 (4)
C21'	1.0425 (6)	0.1890 (6)	0.7686 (5)	0.076 (6)
C22'	1.0064 (6)	0.5508 (6)	-0.0078 (5)	0.088 (5)
C23'	0.9974 (7)	0.4556 (6)	-0.0677 (5)	0.111 (8)

Table 2. *Selected geometric parameters* (Å, °)

O1—C5	1.48 (1)	O1'—C5'	1.44 (1)
O2—C3	1.41 (1)	O2'—C3'	1.43 (1)
O4—C17	1.45 (1)	O4'—C17'	1.44 (1)
C2—C3	1.49 (1)	C2'—C3'	1.49 (1)
C4—C5	1.52 (1)	C4'—C5'	1.55 (1)
C5—C10	1.50 (1)	C5'—C10'	1.46 (1)
C13—C18	1.56 (1)	C13'—C18'	1.51 (1)
C19—C20	1.19 (1)	C19'—C20'	1.19 (1)
O1—C10	1.48 (1)	O1'—C10'	1.46 (1)
O3—C3	1.42 (1)	O3'—C3'	1.42 (1)
C1—C10	1.49 (1)	C1'—C10'	1.49 (1)
C3—C4	1.51 (1)	C3'—C4'	1.54 (1)
C5—C6	1.55 (1)	C5'—C6'	1.50 (1)
C9—C11	1.32 (1)	C9'—C11'	1.33 (1)
C14—C15	1.55 (1)	C14'—C15'	1.54 (1)
C5—O1—C10	60.8 (4)	C5'—O1'—C10'	60.3 (4)
C2—C3—C4	112.0 (6)	C2'—C3'—C4'	112.9 (6)
C4—C5—C10	121.7 (6)	C4'—C5'—C10'	119.4 (6)
O1—C5—C10	59.7 (4)	O1'—C5'—C10'	60.7 (5)
C6—C5—C10	120.8 (6)	C6'—C5'—C10'	122.4 (6)
C5—C10—C9	118.3 (6)	C5'—C10'—C9'	117.6 (6)
O1—C10—C5	59.5 (4)	O1'—C10'—C5'	59.0 (4)
C17—C13—C18	108.5 (6)	C17'—C13'—C18'	109.6 (5)
C14—C13—C17	99.8 (5)	C14'—C13'—C17'	100.7 (5)
O4—C17—C13	111.8 (5)	O4'—C17'—C13'	114.1 (5)
C13—C17—C19	108.9 (6)	C13'—C17'—C19'	110.5 (5)
C19—C20—C21	176.8 (8)	C19'—C20'—C21'	179.2 (7)
C2—C1—C10	112.0 (6)	C2'—C1'—C10'	113.2 (6)
O1—C5—C4	113.3 (6)	O1'—C5'—C4'	113.8 (6)
C4—C5—C6	114.7 (6)	C4'—C5'—C6'	114.7 (6)
O1—C5—C6	112.7 (6)	O1'—C5'—C6'	112.8 (6)
C5—C6—C7	112.2 (5)	C5'—C6'—C7'	112.5 (6)
C1—C10—C5	118.3 (6)	C1'—C10'—C5'	121.3 (6)
O1—C10—C1	114.1 (6)	O1'—C10'—C1'	114.9 (6)
C14—C13—C18	110.5 (6)	C14'—C13'—C18'	111.2 (5)

O4—C17—C16	115.1 (6)	O4'—C17'—C16'	115.5 (6)
C16—C17—C19	111.6 (6)	C16'—C17'—C19'	110.0 (5)
O4—C17—C19	105.5 (5)	O4'—C17'—C19'	104.5 (5)
C10—C1—C2—C3	55.2 (8)	C10'—C1'—C2'—C3'	51.3 (8)
C1—C2—C3—C4	−60.2 (8)	C1'—C2'—C3'—C4'	−56.8 (8)
C2—C3—C4—C5	34.6 (9)	C2'—C3'—C4'—C5'	33.6 (8)
C3—C4—C5—C10	−6.8 (10)	C3'—C4'—C5'—C10'	−4.7 (9)
C4—C5—C10—C1	2.6 (10)	C4'—C5'—C10'—C1'	−0.2 (10)
C2—C1—C10—C5	−25.6 (9)	C2'—C1'—C10'—C5'	−22.5 (9)
C8—C9—C10—C5	−9.6 (10)	C8'—C9'—C10'—C5'	−5.0 (9)
C6—C5—C10—C9	−1.7 (10)	C6'—C5'—C10'—C9'	−0.3 (10)
C10—C5—C6—C7	−18.5 (9)	C10'—C5'—C6'—C7'	−24.2 (9)
C5—C6—C7—C8	50.3 (8)	C5'—C6'—C7'—C8'	53.0 (8)
C6—C7—C8—C9	−62.0 (8)	C6'—C7'—C8'—C9'	−57.6 (7)
C7—C8—C9—C10	39.7 (8)	C7'—C8'—C9'—C10'	33.3 (9)
C9—C11—C12—C13	−16.7 (10)	C9'—C11'—C12'—C13'	−13.9 (10)
C8—C9—C11—C12	0.0 (12)	C8'—C9'—C11'—C12'	−0.8 (11)
C14—C8—C9—C11	−13.6 (10)	C14'—C8'—C9'—C11'	−15.7 (9)
C9—C8—C14—C13	44.6 (8)	C9'—C8'—C14'—C13'	47.2 (8)
C12—C13—C14—C8	−62.4 (7)	C12'—C13'—C14'—C8'	−61.7 (7)
C11—C12—C13—C14	45.5 (8)	C11'—C12'—C13'—C14'	42.4 (8)
C14—C13—C17—C16	−41.3 (6)	C14'—C13'—C17'—C16'	−41.8 (6)
C17—C13—C14—C15	41.8 (6)	C17'—C13'—C14'—C15'	44.2 (6)
C13—C14—C15—C16	−27.1 (7)	C13'—C14'—C15'—C16'	−29.5 (7)
C14—C15—C16—C17	0.3 (7)	C14'—C15'—C16'—C17'	3.0 (7)
C15—C16—C17—C13	25.6 (7)	C15'—C16'—C17'—C13'	24.4 (7)

H atoms were located from difference Fourier maps; they were positioned geometrically and included as riding atoms with fixed isotropic displacement parameters in the structure-factor calculations.

Data collection: Siemens diffractometer software. Cell refinement: Siemens diffractometer software. Data reduction: *SHELXTL-Plus* (Sheldrick, 1990). Program(s) used to solve structure: *SHELXTL-Plus*. Program(s) used to refine structure: *SHELXTL-Plus*. Molecular graphics: *SHELXTL-Plus*. Software used to prepare material for publication: *PARST* (Nardelli, 1983).

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2,4-Diphenylquinoline and its Sterically Hindered Derivative 3-Methyl-2,4-diphenylquinoline

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Abstract

The rotation of the phenyl groups in 2,4-diphenylquinoline, $C_{21}H_{15}N$, and its sterically hindered 3-methyl-2,4-diphenylquinoline derivative, $C_{22}H_{17}N$, are compared. The comparison demonstrates that the orientation of the phenyl substituents has a marked effect on the interpretation of both the ^1H and ^{13}C NMR spectra of these compounds in solution.

Comment

We have recently reported the results of an ^1H and a ^{13}C NMR spectral study of 3-methyl-2,4-diphenylquinoline (Osborne, Ahmet, Miller & Warmsley, 1995). The ^1H spectra were assigned by consideration of the anisotropic effects resulting from the rotation of the phenyl rings. The ^{13}C NMR spectra obtained were interpreted by proposing the existence of a 'pseudo-*peri*-proximity' (PPP) effect. A normal *peri*-proximity effect (Wilson & Stothers, 1974) for the phenyl–methyl couple in the ^{13}C NMR spectrum of 5,8-dimethyl-2,4-diphenylquinoline has been observed previously (Osborne, 1983, 1989).

Here we report the crystal and molecular structures of 2,4-diphenylquinoline, (1), and 3-methyl-2,4-diphenylquinoline, (2), and discuss the effect of the 3-methyl substituent on the crystal structure and ^1H NMR spectrum. Figs. 1 and 2 depict the molecular structures of (1) and (2), respectively, and show the labelling scheme used. Examination of selected bond angles presented in Tables 2 and 4 reveals that all the selected angles are close to 120°, indicating that there is little in-plane splaying of the phenyl rings. Furthermore, there is no out-of-plane distortion of the phenyl groups.